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ORIGINAL REPORT

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

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ABSTRACT

Purpose
This multicenter study, to our knowledge, is the first phase III trial to compare trabectedin versus dacarbazine in patients with advanced liposarcoma or leiomyosarcoma after prior therapy with an anthracycline and at least one additional systemic regimen.

Patients and Methods
Patients were randomly assigned in a 2:1 ratio to receive trabectedin or dacarbazine intravenously every 3 weeks. The primary end point was overall survival (OS), secondary end points were disease control—progression-free survival (PFS), time to progression, objective response rate, and duration of response—as well as safety and patient-reported symptom scoring.

Results
A total of 518 patients were enrolled and randomly assigned to either trabectedin (n = 345) or dacarbazine (n = 173). In the final analysis of PFS, trabectedin administration resulted in a 45% reduction in the risk of disease progression or death compared with dacarbazine (median PFS for trabectedin v dacarbazine, 4.2 v 1.5 months; hazard ratio, 0.55; $P < .001$); benefits were observed across all preplanned subgroup analyses. The interim analysis of OS (64% censored) demonstrated a 13% reduction in risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin v dacarbazine, 12.4 v 12.9 months; hazard ratio, 0.87; $P = .37$). The safety profiles were consistent with the well-characterized toxicities of both agents, and the most common grade 3 to 4 adverse effects were myelosuppression and transient elevation of transaminases in the trabectedin arm.

Conclusion
Trabectedin demonstrates superior disease control versus conventional dacarbazine in patients who have advanced liposarcoma and leiomyosarcoma after they experience failure of prior chemotherapy. Because disease control in advanced sarcomas is a clinically relevant end point, this study supports the activity of trabectedin for patients with these malignancies.

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INTRODUCTION

After GI stromal tumors, leiomyosarcomas and liposarcomas are the most common subtypes of soft tissue sarcomas (STS), a heterogeneous group of malignancies that arise from tissues of mesenchymal origin and together compose approximately 1% of all solid tumors.[1,2]

The prognosis for patients with advanced or metastatic STS is poor, with an estimated median survival of 12 to 15 months.[3-5] Treatment is palliative in nature, and the goal is delay of the progression and severe morbidity that can arise when tumor growth compromises organ function.[6] Initial therapy for patients with STS that is unresectable for cure typically includes cytotoxic chemotherapy that is most commonly anthracycline based (mainly doxorubicin) or gemcitabine based.[7,8] Other chemotherapeutic agents, including dacarbazine, ifosfamide, and unapproved analogs, have been investigated.[9-13] In metastatic STS, combination chemotherapy with dose-intensive doxorubicin

plus ifosfamide improves response rates and disease control compared with doxorubicin alone but with increased severe toxicities and without overall survival benefit.[5] The activities of single-agent dacarbazine and ifosfamide in this clinical setting have been used by the European Organization for Research and Treatment of Cancer as a reference to assess the activity of novel agents in STS (3- and 6-month progression-free rates [PFRs] of 39% and 14%, respectively).[14] These thresholds have been used to assess the activity of trabectedin in phase II studies[15] and to identify the target population for the pivotal phase III study of pazopanib.[16,17]

Trabectedin, a marine-derived drug, has a complex mechanism of action that affects key cell biology processes in tumor cells and the tumor microenvironment through direct effects on tumor-associated macrophages and tissue-resident histiocytes.[18-20] It binds to the minor groove of DNA, which thereby affects the function of DNA binding proteins, including transcription factors and DNA repair machinery, to result in perturbation of the cell cycle and induction of p53-independent apoptosis.[21,22] In several phase II trials, trabectedin exhibited activity in patients with metastatic STS,[23-25] and a randomized trial to test two different doses and schedules of trabectedin led to the first regulatory approval in 2007.[15] The present multicenter study was conducted to compare the efficacy and safety of trabectedin versus dacarbazine in a randomized phase III trial in patients with advanced liposarcoma or leiomyosarcoma.

PATIENTS AND METHODS

Patients

Patients were eligible if they were age 15 years or older; had unresectable, locally advanced or metastatic liposarcoma or leiomyosarcomas; and were previously treated with at least either a combination of an anthracycline and ifosfamide or an anthracycline plus one or more additional cytotoxic chemotherapy regimen(s). Patients required adequate bone marrow, renal, and liver functions, and an Eastern Cooperative Oncology Group performance status score of 1 or lower. Exclusion criteria included known CNS metastasis, myocardial infarct within 6 months before enrollment, and New York Heart Association class II or greater heart failure. Review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki, the

International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. All patients provided written informed consent to participate on the study.

Study Design and Treatment

This phase III trial (NCT01343277, also coded as ET743-SAR-3007) is a randomized, open-label, active-controlled, parallel-group, multicenter study implemented at 85 sites in four countries. Patients were randomly assigned in a 2:1 ratio to receive either trabectedin at a starting dose of 1.5 mg/m^2 as a 24-hour intravenous (IV) infusion or dacarbazine at a starting dose of 1 g/m^2 as a 20- to 120-minute IV infusion. Study drug was administered on day 1 of each 21-day treatment cycle. All trabectedin doses were administered via central IV access after premedication with dexamethasone 20 mg IV. Criteria for dose reductions and dose delays, in case of treatment-associated toxicities, were standardized in the protocol.

The primary study end point was overall survival (OS); secondary end points assessed disease control and included progression-free survival (PFS), time to progression, objective response rate (ORR), and duration of response (DOR). The end points of clinical benefit rate[26] (CBR; defined as the sum of complete responses + partial responses [PR] + stable disease for at least 18 weeks) and duration of stable disease were added to the statistical analysis plan as preplanned analyses to describe those patients who experienced prolonged disease control.

The study was designed with a preplanned interim analysis of the primary end point of OS, which was to occur concurrently with the final analysis of PFS, at 188 death events. The clinical cutoff date of September 16, 2013, was prospectively determined on the basis of anticipation of the required number of death events.

Assessments

Monitoring of study participant survival was performed and used to calculate OS. Investigators assessed tumor response by radiographic imaging of the chest, abdomen, and pelvis every 6 weeks for the first 36 weeks on study and every 9 weeks thereafter until disease progression, subsequent anticancer therapy, or patient death occurred. The PFS end point was validated through an audit by independent radiologists, who were blinded to treatment assignment and who assessed radiographic PFS (rPFS) in a subset of approximately 60% of the study population. Safety assessments were based on observed adverse events, clinical laboratory tests, vital sign measurement, physical examination, cardiac function (using multigated acquisition scan or echocardiogram), and concomitant medication use.
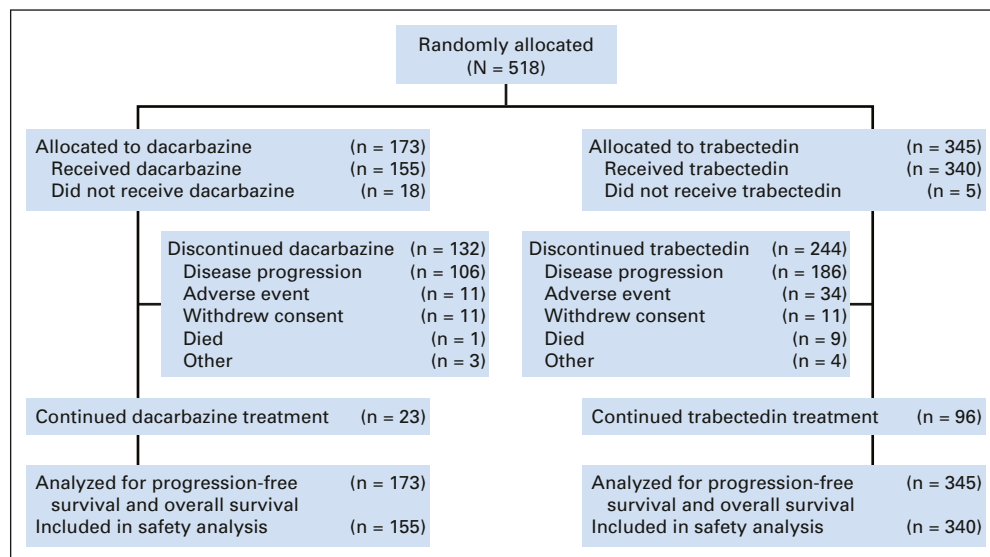

Fig 1. CONSORT diagram.

Statistical Analyses

The primary statistical methodology for comparison of treatment effectiveness for OS, PFS, and DOR was the unstratified log-rank test. A Cox proportional hazard model was used to examine the effect of the prognostic factors. The statistical methodology for ORR and CBR was Fisher's exact test. To detect a difference between a median OS of 10 months in the dacarbazine group and a median OS of 13.5 months in the trabectedin group (hazard ratio [HR], 0.74) at an overall two-sided significance level of .05 with a power of 80% required 376 events. A sample size of 570 patients was planned with an interim analysis for OS after 50% of events. The cumulative α spent was to be .003 and .047 for the interim and final OS analyses, respectively. This study used a group sequential method with the O'Brien-Fleming boundaries, as implemented by the Lan-DeMets α spending function.

One analysis of PFS was planned at the time of the OS interim analysis after a projected 331 PFS events, which provided at least 90% power to detect an HR of 0.667 (median PFS for dacarbazine v trabectedin arms, 2.50 v 3.75 months, respectively) with a two-sided significance level of .05. Final PFS and ORR data, after recommendations of the independent data monitoring committee, were submitted for regulatory consideration while the study continued toward the final analysis for OS. The results of the overall estimate of HR for rPFS, which were based on an independent audit, were calculated as proposed by the method of Dodd.[27] The upper limit for the 95% CI was compared with 1.

RESULTS

Patients and Treatment

Between May 27, 2011, and the September 16, 2013, clinical cutoff for the interim analysis of the primary end point of OS, 518 of 570 planned patients were randomly assigned to receive either trabectedin (n = 345) or dacarbazine (n = 173; Fig 1) and are included in this interim analysis. Enrollment was ongoing at the time of the clinical cutoff. Baseline demographic and disease characteristics were well balanced (Table 1). The study population was heavily pretreated; 88% had at least two previous lines of systemic therapy, greater than 90% had previous surgery, and 50% had prior radiotherapy. The median time from last disease progression was less than 1 month in both treatment groups (0.85 v 0.82 months, respectively), and a majority (58%) reported progressive disease as the best response to their previous line of therapy.

Time on Study Treatments

At the time of interim analysis, the proportion of patients in the trabectedin arm still receiving study treatment was nearly double that in the dacarbazine arm (28% v 15%, respectively). Disease progression was the most common reason for discontinuation of study treatment regardless of treatment group (trabectedin v dacarbazine, 55% v 68%). Discontinuation resulting from toxicity, including adverse events and death, occurred in 12.6% and 7.7% of the trabectedin and dacarbazine groups, respectively. Withdrawal of consent occurred twice as frequently in the dacarbazine group, by 3.2% patients in the trabectedin group versus by 7.1% in the dacarbazine group.

The median number of cycles received in the trabectedin group was twice that of the dacarbazine group (4 v 2 cycles, respectively), and increased exposure rates were noted at both six cycles (34% v 17%, respectively) and 12 cycles (10% v 2%, respectively). Cycle delays or dose reductions were reported in 57% and 35% of patients in the

| Table 1. Baseline Demographic and Disease Characteristics		
	No. (%) of Patients	
Variable	Trabectedin (n = 345)	Dacarbazine (n = 173)
Age, years		
Median (range)	57 (18.0-81.0)	56 (17.0-79.0)
Sex		
Male	107 (31)	47 (27)
Female	238 (69)	126 (73)
Baseline BMI, kg/m^2		
Median (range)	28.21 (14.5-78.1)	27.05 (13.3-66.7)
Histology		
Leiomyosarcoma	252 (73)	126 (73)
Uterine	134 (39)	78 (45)
Nonuterine	118 (34)	48 (28)
Liposarcoma	93 (27)	47 (27)
Myxoid ± round cell	38 (11)	19 (11)
Pleomorphic	10 (3)	3 (2)
Dedifferentiated	45 (13)	25 (15)
Baseline ECOG performance status score		
0	171 (50)	86 (50)
1	174 (50)	87 (50)
Lines of prior chemotherapy		
1	38 (11)	23 (13)
2	160 (46)	75 (43)
3	87 (25)	43 (25)
4	37 (11)	21 (12)
> 4	23 (7)	11 (6)
Best response to last line of previous chemotherapy		
Complete response	4 (1)	3 (2)
Partial response	28 (8)	14 (8)
No change (stable disease)	114 (33)	51 (30)
Progression of disease	198 (57)	103 (60)
Unknown/missing	1 (0)	2 (1)
Previous surgery for malignancy		
Yes	327 (95)	158 (91)
No	18 (5)	15 (9)
Previous radiotherapy for malignancy		
Yes	176 (51)	80 (46)
No	169 (49)	93 (54)
Time from initial diagnosis to random assignment, months		
Median (range)	33.94 (2.5-318.5)	27.10 (1.6-267.1)
Time from last disease progression to random assignment, months		
Median (range)	0.85 (0.0-13.7)	0.82 (0.1-9.8)

NOTE. Percentages were calculated with the number of patients randomly assigned to each treatment group as the denominator.
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

trabectedin group, respectively, compared with 40% and 10% of patients in the dacarbazine group (Appendix Table A1, online only).

Efficacy

The final analysis of PFS, performed after 329 PFS events, showed that treatment with trabectedin resulted in a 45% reduction in the risk of disease progression or death compared with dacarbazine (HR, 0.55; 95% CI, 0.44 to 0.70; P < .001; Fig 2A). Improved disease control by trabectedin was discernible at the time of the first planned disease
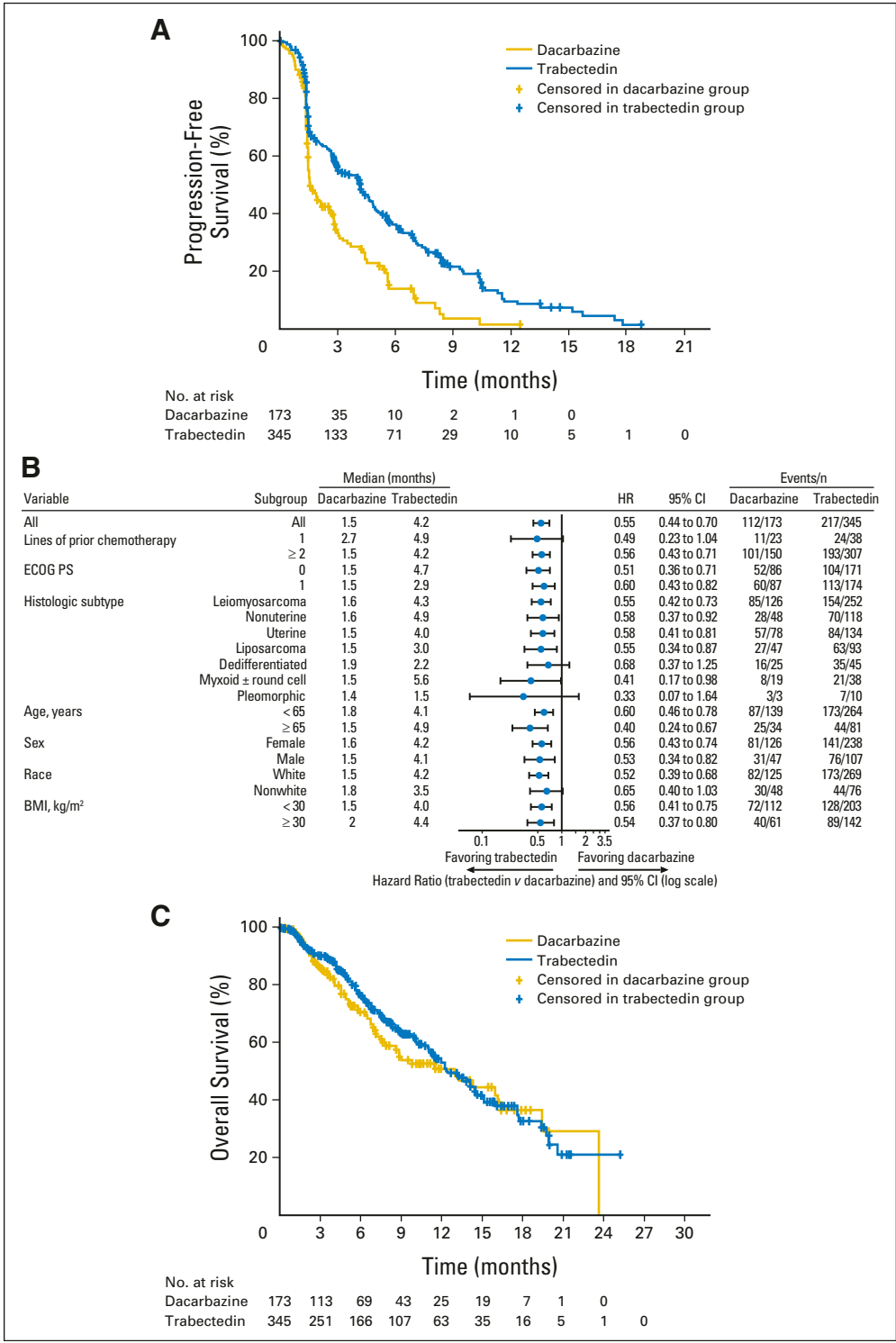
Fig 2. Kaplan-Meier estimates of progression-free survival, subgroup analyses, and overall survival at the interim analysis. (A) Progression-free survival; (B) subgroup analysis (hazard ratios [HRs] and 95% CIs) of progression-free survival; and (C) overall survival. HR was calculated as the hazard in the trabectedin treatment group divided by the hazard in the dacarbazine treatment group. BMI, body mass index.

assessment (6 weeks), which led to an improved median PFS in the trabectedin group (4.2 months v 1.5 months with dacarbazine). PFRs at 3 and 6 months were 56% and 37% in the trabectedin arm versus 34% and 14% in the dacarbazine arm. The PFS treatment benefit with trabectedin was consistently observed across all 19 preplanned subgroups examined in sensitivity analyses (Fig 2B), and equivalent benefits were observed across the two sarcoma subtypes (HR, 0.55 each for patients with leiomyosarcoma and for patients with liposarcoma).

To validate the investigator assessment of PFS, an audit was conducted by independent radiologists who were blinded to treatment assignment. The rPFS of the entire study population, and of the audited and unaudited subgroups, was calculated by using

Table 2. Summary of Key Progression-Free Survival/Radiographic Progression-Free Survival Results

Variable	Survival Measure					
	PFS-INV (n = 518)	rPFS-INV (n = 518)	rPFS-INV (audited subset; n = 304)	rPFS-INV (unaudited subset; n = 214)	rPFS-IR (audited subset; n = 304)	rPFS-IR (overall estimate)
HR*	0.55	0.57	0.58	0.54	0.55	0.54
95% CI	0.44 to 0.70	0.45 to 0.72	0.43 to 0.79	0.37 to 0.80	0.40 to 0.75	0.41 to 0.71

Abbreviations: HR, hazard ratio; INV, investigator assessed; IR, independent radiologist; PFS, progression-free survival; rPFS, radiographic progression-free survival.
*The HR was calculated as the hazard in the trabectedin treatment group divided by the hazard in the dacarbazine treatment group.

investigator assessment; then, the rPFS was calculated for the audited subgroup by using the independent radiologists' assessments (Table 2). The independent assessment of the rPFS of the audited subset (HR, 0.55) was used to provide an estimate of the HR for rPFS of the entire population by using an adaptation of a previously reported method[27] (HR, 0.54; 95% CI, 0.41 to 0.71), which was consistent with the investigator assessment.

Best responses experienced by both treatment groups, as well as their durations, are summarized in Table 3. There were no complete responses in either treatment group. PRs were more frequently observed within the trabectedin group (ORR, 9.9% v 6.9%; $P = .33$). The median DOR within the trabectedin group was approximately 50% greater than in the dacarbazine group (6.5 v 4.2 months, respectively; $P < .14$). Stable disease as best response was more frequently achieved in the trabectedin group (51% v 35%), and the median duration of stable disease was significantly improved in the trabectedin arm (6.0 v 4.2 months; $P < .001$). The clinical benefit rate, which reflects both objective disease response and durable stable disease, was significantly higher in the trabectedin group (34% v 19%; $P < .001$; Table 3).

The interim analysis occurred as planned at 50% of the total events required for the final analysis of OS (ie, 189 death events). The median duration of survival follow-up time was 8.6 months. Although the OS data at this interim analysis were highly censored (64%), the results favored the trabectedin group, with an overall 13% reduction in risk of death (median OS of trabectedin v dacarbazine, 12.4 months v 12.9 months; HR, 0.87; $P = .37$; Fig 2C). Subsequent anticancer therapy was less frequently used in the trabectedin arm (47% v 56%, respectively) and occurred significantly later after study entry (median time to initiation from random assignment for trabectedin versus dacarbazine, 6.9 v 3.7 months; HR, 0.47; 95% CI, 0.36 to 0.61; $P < .001$). The most frequently used subsequent therapy in both arms (trabectedin v dacarbazine) was pazopanib (18% v 28%,

respectively), which was followed by radiation (10% v 15%, respectively), gemcitabine (9% v 15%, respectively), and dacarbazine (17% v 6%, respectively; Table 4).

Safety

The adverse events of the study were consistent with the well-characterized safety and toxicity profiles of both study drugs. The most common adverse events were predominantly of grade 1 to 2 severity (Table 5). Grade 3 to 4 toxicities were primarily observed in laboratory-based measures of myelosuppressive toxicity (in both treatment groups) and transient transaminase elevations (in the trabectedin group). Less often, grade 3 to 4 creatine phosphokinase elevations were seen with trabectedin treatment (5.3% v 0.6% in the dacarbazine group), and 1.2% of patients who received trabectedin experienced rhabdomyolysis.

The incidence of patients who died within 60 days of the first dose of study drug was similar in both treatment arms (7.1% v 5.8% in trabectedin v dacarbazine arms, respectively), whereas treatment-related deaths (n = 7; 2.1%) were only reported in the trabectedin group. These deaths were related to sepsis/septic shock (n = 3), rhabdomyolysis/sepsis (n = 1), renal failure (n = 1), renal failure/cardiac arrest (n = 1), or multiorgan failure (n = 1).

DISCUSSION

This multicenter, randomized, international, phase III clinical trial confirms prior experience in smaller trials that documented the efficacy of trabectedin in the control of advanced STS after failure of prior cytotoxic chemotherapy. The patients studied were heavily pretreated, having experienced failure of previous systemic therapy, surgery, and radiation therapy, and they had rapidly progressing disease. Within

Table 3. End Points That Reflect Disease Control

End Point	Trabectedin (n = 345)	Dacarbazine (n = 173)	HR/OR (95% CI)*	P
PFS, months	4.2	1.5	0.55 (0.44 to 0.70)	< .001
TTP, months	4.2	1.5	0.52 (0.41 to 0.66)	< .001
No. (%) of ORR	34 (9.9)	12 (6.9)	1.47 (0.72 to 3.2)	.33
DOR, months	6.5	4.2	0.47 (0.17 to 1.32)	.14
No. (%) with SD as best response	177 (51)	60 (35)	—	—
Duration of SD, months	6.01	4.17	0.45 (0.30 to 0.67)	< .001
% of CBR	34	19	2.3 (1.45 to 3.7)	< .001

Abbreviations: CBR, clinical benefit rate; DOR, duration of response; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; SD, stable disease; TTP, time to progression..
*The HR was calculated as the hazard in the trabectedin treatment group, divided by the hazard in the dacarbazine treatment group.

Table 4. Selected Subsequent Anticancer Therapy		
	No. (%) of Patients	
Therapy	Trabectedin (n = 345)	Dacarbazine (n = 173)
Total with subsequent anticancer chemotherapy	162 (47)	97 (56)
Pazopanib	63 (18)	48 (28)
Dacarbazine	60 (17)	11 (6)
Radiation	35 (10)	25 (15)
Gemcitabine	30 (9)	25 (15)
Surgery	23 (7)	17 (10)
Docetaxel	19 (6)	21 (12)
Ifosfamide	7 (2)	10 (6)
Doxorubicin	9 (3)	5 (3)
Eribulin	9 (3)	1 (1)
Trabectedin	1 (< 1)	4 (2)

NOTE. Subsequent anticancer therapies that were used for at least 5% of patients in either treatment group were included. In addition, doxorubicin, eribulin, and trabectedin were also included on the basis of their previously demonstrated activities.

of the chimeric FUS-CHOP translocation-generated oncoprotein that has transcriptional regulatory activity in these tumors.[31-33]

The benefit of trabectedin versus dacarbazine treatment was also supported by other secondary end points, with improvements in both the ORR (9.9% v 6.9%, respectively), and the median duration of responses (6.5 v 4.2 months, respectively). Importantly, the majority of patients who benefited from trabectedin experienced stable disease as their best response, at an increased rate than that observed with dacarbazine (51% v 35%) and for significantly increased durations. The CBR, which included objective disease shrinkage (which consisted of PRs in this trial) and durable stable disease (ie, > 18 weeks in duration), also documents the anticancer activity of trabectedin, because nearly twice the proportion of patients who received trabectedin versus those who received dacarbazine achieved this end point in this randomized study (34% v 19%, respectively). The therapeutic benefit of continued disease control with extended trabectedin dosing beyond six cycles has been reported in a recent study as well.[34]

The safety and tolerability of these study drugs were consistent with extensive prior experience and reports.[11,12,15,35] Laboratory abnormalities were the most frequently reported grade 3 to 4 adverse events in this study; were generally transient and noncumulative; and were managed by dose delays, reductions, supportive care, and, if required, treatment discontinuations. Although this study demonstrates that toxicity was increased in the trabectedin arm, trabectedin is regarded as a generally well-tolerated agent relative to other sarcoma treatment options, with low rates of mucositis and alopecia and no cumulative toxicities that limit treatment duration. Consistent with this profile, a greater proportion of patients in the trabectedin arm than in the dacarbazine arm were able to receive prolonged courses of therapy. Extensive clinical experience with trabectedin outside the United States in standard practice has supported its reputation as a generally well-tolerated agent with no cumulative toxicities, which was again demonstrated in this study.[35-38]

this high-risk population, trabectedin administration resulted in a statistically significant 45% reduction in the risk of disease progression or death versus the active control therapy, dacarbazine ($P < .001$). This benefit in disease control was observed regardless of disease histology; previous lines of systemic therapy; or clinical considerations, such as age, sex, ethnicity, or baseline performance status. Of note, the greatest increase in median PFS (5.6 months v 1.5 months with trabectedin v dacarbazine, respectively) was observed within the myxoid/round cell liposarcoma subgroup (Fig 2B), which is consistent with the early identification of this uniquely sensitive STS subtype[25,28] and similar to a recent report of trabectedin activity in patients with translocation-related sarcomas.[29,30] This is also highly consistent with the proposed action of trabectedin as a direct inhibitor

Table 5. Most Common Adverse Events						
	No. (%) Adverse Events by Treatment and Grade					
	Trabectedin (n = 340)			Dacarbazine (n = 155)		
Adverse Event	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Nausea	247 (73)	18 (5)	0	76 (49)	3 (2)	0
Fatigue	228 (67)	20 (6)	0	79 (51)	2 (1)	1 (1)
Neutropenia	165 (49)	70 (21)	56 (16)	45 (29)	17 (11)	15 (10)
Alanine aminotransferase increased	154 (45)	85 (25)	4 (1)	9 (6)	1 (1)	0
Vomiting	149 (44)	16 (5)	0	33 (21)	2 (1)	0
Anemia	134 (39)	49 (14)	0	45 (29)	17 (11)	1 (1)
Constipation	121 (36)	3 (1)	0	44 (28)	0	0
Aspartate aminotransferase increased	120 (35)	40 (12)	4 (1)	8 (5)	0	0
Decreased appetite	116 (34)	7 (2)	0	31 (20)	0	1 (1)
Diarrhea	115 (34)	6 (2)	0	35 (23)	0	0
Thrombocytopenia	101 (30)	27 (8)	31 (9)	56 (36)	15 (10)	13 (8)
Dyspnea	84 (25)	12 (4)	1 (< 1)	30 (19)	1 (1)	0
Peripheral edema	83 (24)	3 (1)	0	21 (14)	1 (1)	0
Headache	78 (23)	1 (< 1)	0	29 (19)	0	0
Blood alkaline phosphatase increased	69 (20)	5 (1)	0	11 (7)	0	0
Cough	61 (18)	1 (< 1)	0	32 (21)	0	0

NOTE. Most common adverse events occurred with ≥ 20% frequency.

The 3- and 6-month PFRs observed in this study provide historical context to these results, which are consistent with earlier studies with both agents. The 3- and 6-month PFRs of dacarbazine (34% and 14%, respectively) were consistent with the European Organization for Research and Treatment of Cancer criteria established to define active agents in unselected STS (39% and 14%, respectively) and with a recent phase II study in patients with unselected STS.[12] This level of activity across multiple studies suggests that the activity of dacarbazine is similar across sarcoma study populations (ie, liposarcoma or leiomyosarcoma with selected and unselected histologies) and justifies its selection as the active comparator in this study.

In this study, 3- and 6-month PFRs of trabectedin (56% and 37%, respectively) confirm the higher level of anticancer activity of trabectedin in patients with leiomyosarcoma and liposarcoma, which was also observed in a prior randomized, phase II study (52% and 36%, respectively).[15] The confirmation of activity within this patient population provides an additional treatment option for patients who have limited systemic options, given the lower ifosfamide efficacy in patients with leiomyosarcoma[5,39] and the relative lack of efficacy of pazopanib in patients with liposarcoma.[16] Furthermore, the favorable efficacy observed in patients older than 65 years, with a safety profile similar to that observed in younger patients (data not shown), confirms the results of earlier analyses[40] that suggest that trabectedin is an important treatment option for a group of patients who are often excluded from treatment with doxorubicin-based regimens.[5]

The interim analysis of OS, the primary end point of this study, demonstrated a statistically nonsignificant 13% reduction in risk of death that favored the trabectedin group. Of note, the median OS in the dacarbazine arm was statistically equivalent to the trabectedin group and exceeded the predefined statistical assumption of 10 months; this may reflect the use of subsequent therapies, including pazopanib, which was approved by regulatory agencies for STS during the conduct of this trial. Although the study continued per protocol for the final analysis of OS, the results of two recently reported phase III studies have illustrated the difficulty in prolonging OS, despite robust improvements in PFS, even when the control arm involves a placebo.[5,17] Given the historical difficulty in demonstrating OS improvement, the clinical documentation of disease control, measured as PFS and CBR, has been proposed as a measure of clinically relevant efficacy in advanced sarcomas.[26] The results of this large, randomized trial support the activity of trabectedin as an effective anticancer agent in this population of patients who have rare but life-threatening malignancies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

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Table A1. Treatment Cycle Delays and Dose Reductions		
	No. (%) of Patients	
Cycle or Dose Variable	Trabectedin (n = 340)	Dacarbazine (n = 155)
Total with at least two cycles	298 (88)	125 (81)
Cycle delay		
Yes	193 (57)	62 (40)
No	105 (31)	63 (41)
No. of cycle delays		
1	96 (28)	35 (23)
2	37 (11)	13 (8)
3	27 (8)	8 (5)
4	12 (4)	1 (1)
≥ 5	21 (6)	5 (3)
Dose reduction		
Yes	119 (35)	15 (10)
No	179 (53)	110 (71)
No. of dose reductions		
1	83 (24)	13 (8)
2	36 (11)	2 (1)
NOTE. Cycle delays and dose reductions were tabulated for patients who received at least two cycles of treatment.		